REMARKS

I. REQUEST FOR RECONSIDERATION OF RESTRICTION REQUIREMENT

Claims 1-8 and 10-18 are currently pending; claim 1 has been examined. A copy of all claims as they would appear after entry of the present amendment is attached hereto as **Exhibit A**.

Applicants respectfully request further reconsideration of the restriction requirement and solicit the Examiner's discretion with respect to examining claims 2-8 (Group II) and 10-18 (group III) together with claim 1. As explained in further detail below, the specification does disclose and claim the use together of the inventions of groups I and III. In response to the Examiner's stated concern that the set of claim 1 cannot be used in the methods of claim 2 or 10, Applicants have amended claim 2 to recite that the enzymatic test kit used according to the method is the enzymatic test kit of the set of claim 1, and have similarly amended claim 10 to recite that the DNA sequence used according to the method is the DNA sequence of the set of claim 1.

Applicants note that if claim 1 is deemed allowable, all claims dependent from claim 1, which include all of the limitations of this linking claim, should be entitled to examination and should be deemed allowable. See MPEP §809.03. In particular, claims 10-14 and 16 are patentable if the selected DNA sequences recited in claim 1 are deemed patentable. *See In re Pleuddemann*, 910 F.2d 823, 15 USPQ 2d 1738, 1741 (Fed. Cir. 1990), wherein the Court of Appeals for the Federal Circuit held that a method of using a novel compound is patentable because the method of using the novel compound is considered part of the properties of the compound.

II. OBJECTIONS TO SPECIFICATION AND OTHER FORMAL MATTERS

The specification has been amended to address the Examiner's objections to the format thereof. A brief description of the drawings has been inserted and the specification has been amended to recite the sequence identifiers corresponding to each sequence. In addition, the specification has been amended to correct the typographical error noted by the Examiner at page 4 and in claim 1 with respect to the nucleotide sequence of "AlaDH-F2."

Applicants note that the sequence listing as filed is correct and consequently no response to the Notice to Comply with sequence listing requirements is needed.

Applicants also provide herewith a certified copy of European patent appl. no. 97 101 338.8.

III. THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner rejected claim 1 under 35 U.S.C. §112, first paragraph, as assertedly lacking written description. In response, the Applicants submit that ample support for amended claim 1 is found in the examples and claims as originally filed. Contrary to the Examiner's assertion that the specification does not disclose a method in which the claimed combination of components is employed, original claim 14 describes a "method according to claim 2 ***and/or*** claim 10. [Emphasis added.]" Both claim 2 and claim 10 described a method for the "diagnosis of tuberculosis and other mycobacterial infections" in "humans and animals;" claim 2 recited measurement of the activity of alanine dehydrogenase with an enzymatic test kit, while claim 10 recited "use of a DNA sequence according to claim 9 [which recited the DNA sequences now in claim 1]." Thus, the original claims were directed to a method in which a combination of the enzymatic and DNA components of the set of claim 1 is employed.

Moreover, the examples show use of both the enzymatic and the DNA components of the set of claim 1 on samples of the same strains of *Mycobacteria*, to differentiate between pathogenic and non-pathogenic strains. For example, pages 21-24 show classification of strains according to their alanine dehydrogenase enzymatic activity, and pages 26-28 show classification of strains according to whether alanine dehydrogenase gene fragments could be amplified and detected.

Thus, the specification provides ample written description for claim 1 as amended and the rejection under 35 U.S.C. §112, first paragraph may properly be withdrawn.

II. THE REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner rejected claim 1 under 35 U.S.C. §112, second paragraph, as assertedly indefinite in its recitation of a "set," a "DNA sequence" without reference to a DNA molecule or fragment, and the phrase "the following partial sequences and other partial sequences."

In response, the Applicants respectfully submit that the term "set for the diagnosis of tuberculosis and other mycobacterial infections in humans and animals" as

recited in claim 1 is adequately defined by both structural and functional properties. Each of the chemical components of the set is described by its chemical name or structure, and the overall function of the set (diagnosis of tuberculosis and other mycobacterial infections) is also recited in claim 1. The set need not take a particular structural form; it could encompass, e.g., a packaged kit comprising both the enzymatic test kit components and the nucleic acid components, or separately packaged kits sold together, or a laboratory set up that processes clinical samples for both enzymatic activity and DNA detection.

In response to the Examiner's other objections, the term "DNA sequence" has been replaced with a reference to a molecule, *i.e.*, a nucleic acid; the references to "and other partial sequences" and Figure 2.5 have been removed; and the typographical error in the sequence of AlaDH-F2 has been corrected.

III. THE REJECTION UNDER 35 U.S.C. §103(a)

The Examiner rejected claim 1 under 35 U.S.C. §103(a) as assertedly obvious over Katsumata et al., U.S. Patent No. 5,559,016 ("the Katsumata patent") in view of Ahern, The Scientist 9:20 (1995) ("the Ahern publication"). It was the Examiner's position that the Katsumata patent teaches cloning bacterial alanine dehydrogenase genes that would be "hybridizable with" any of the sequences of claim 1 under conditions of sufficiently low stringency, and that the Katsumata patent also teaches confirmation of enzymatic activity with a stain comprising the same components as the enzymatic test kit of claim 1. Although the Examiner admitted that the Katsumata patent did not teach packaging the components into a set or a kit as recited in claim 1, it was asserted that packaging components in a kit is obvious from Ahern.

In response, Applicants respectfully submit that the nucleic acids of the set of claim 1 are not merely fragments of an L-alanine dehydrogenase gene from any microorganism but instead are specific nucleic acid fragments that have the unexpected property of being able to distinguish between pathogenic and non-pathogenic strains of *Mycobacteria*. See, e.g., page 27, lines 17-20 (stating that the gene was present in all *M. tuberculosis* strains). Claim 1 as amended clarifies that the nucleic acid components of the kit are hybridizable with the recited sequences "under stringent conditions" as described and exemplified in section 3.2.1 at pages 24-28.

In contrast, it would not be possible to use the nucleic acids disclosed in the Katsumata patent to distinguish between pathogenic and non-pathogenic organisms; thus, the nucleic acids taught by the art do not have the unexpected property of the nucleic acids of claim 1.

There is no suggestion or motivation to combine Katsumata with Ahern to make the set of claim 1. Moreover, even if combined, the two references do not render obvious the claimed invention because the general discussion in Ahern regarding kits does not suggest the unexpected property of the nucleic acids of the set of claim 1.

The Examiner also rejected claim 1 over Andersen et al., *Infection Immunity*, 60:2317 (1992) ("the Anderson publication") in view of Ahern. However, while the Andersen publication does disclose an (incorrect) nucleotide sequence of the L-alanine dehydrogenase gene of *Mycobacterium tuberculosis*, it does not teach the unexpected property of being able to distinguish between pathogenic and non-pathogenic strains of *Mycobacteria* and does not teach or suggest that it would have been possible to distinguish between non-pathogenic and pathogenic strains by means of such nucleic acids of the set of claim 1. There is also no suggestion or motivation to combine Andersen with Ahern, and the two references even if combined do not suggest the unexpected property of the nucleic acids of the set of claim 1.

Thus, the rejection under 35 U.S.C. §103(a) may properly be withdrawn because the invention is not obvious over the cited art.

CONCLUSION

Claims 1-8 and 10-18 are believed to be allowable in view of the above amendments and remarks, and an early notice thereof is respectfully solicited.

Respectfully submitted,

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EXHIBIT A

Currently pending claims

1. (Twice Amended) A set for the diagnosis of tuberculosis and other mycobacterial infections in humans and animals comprising:
(i) an enzymatic test kit for the determination of the activity of alanine dehydrogenase (E.C. 1.4.1.1), comprising L-alanine, nicotinamide adenine dinucleotide (oxidized form; NAD^+), phenazine methosulphate (PMS) and nitroblue tetrazolium chloride (NBT); and
(ii) a nucleic acid consisting essentially of the DNA sequence selected from the group consisting of the following partial sequences ~~[and other partial sequences]~~ of the alanine dehydrogenase gene of *M. tuberculosis* ~~[(Fig. 2.5)]~~:

Name	Sequence	Orientation
AlaDH-F1	5'-ATGCGCGTCGGTATTCCG-3'	forward
AlaDH-F1+	5'-GCGCGTCGGTATTCCGACCG-3'	forward
AlaDH-F2	5'-GAGACCAAAAAACAACGAA-3'	forward
AlaDH-F4	5'-GAATTCCCATCAGCAATCTTGCAGA-3'	forward
AlaDH-F5	5'-GCCCCGATGAGCGAAGTC-3'	forward
AlaDH-F6	5'-GGGGCCGTCCTGGTGCC-3'	forward
AlaDH-F7	5'-GACGTCGACCTACGCGCTGAC-3'	forward
AlaDH-R1	5'-CTCGGTGAACGGCACCCC-3'	reverse
AlaDH-R2	5'-GGCCAGCACGCTGGCGGG-3'	reverse
AlaDH-R3	5'-CACCCGTTCGGACAGTAA-3'	reverse
AlaDH-R4	5'-CGCGGCCGACATCATCGC-3'	reverse
AlaDH-R5	5'-GGCCGACATCATCGCTTCCC-3'	reverse
AlaDH-R6	5'-CGAGACTAATTTGGGTGCCTTGGC-3'	reverse
AlaDH-R7	5'-ATTTGGGTGCCTTGGC-3'	reverse
AlaDH-RM	5'-GGCGGCGAGTCGACCGGC-3'	reverse

partial sequences thereof and sequences that are hybridizable therewith under stringent conditions, for the diagnosis of tuberculosis and other mycobacterial infections in humans or animals.

2. (Amended) A method for the diagnosis of tuberculosis and other mycobacterial infections of humans and animals, comprising the step of measuring the activity of alanine dehydrogenase (E.C. 1.4.1.1.) with an enzymatic test kit of said set according to claim 1.

3. (Amended) A method according to claim 2, comprising the steps of
(i) isolating possible tuberculosis pathogens,
(ii) making a crude cell extract,
(iii) incubating the extract in solution, and
(iv) measuring the absorption.

4. (Amended) A method according to claim 2 comprising the steps of subjecting clinical samples directly to tuberculosis diagnosis and measuring the alanine dehydrogenase activity.

5. (Amended) A method according to claim 2, comprising the step of differentiating at least one of cells, strains and species of disease-causing organisms (mycobacteria) from non-virulent cells and strains.

6. (Amended) A method according to claim 5, comprising the steps of identifying and differentiating at least one of cells, strains and species of disease-causing organisms of the *M. tuberculosis* complex.

7. (Amended) A method according to claim 2, wherein said steps are carried out in the presence of substances that inhibit at least one of tuberculosis and other mycobacterial infections of humans and animals and optionally recovering said inhibiting substances.

8. (Amended) A method according to claim 2, wherein said steps are carried out

(i) to control epidemics and/or

(ii) after vaccinations (vaccination follow-up) in humans or animals.

10. (Amended) A method for the diagnosis of tuberculosis and other mycobacterial infections in humans and animals comprising the step of using said DNA sequence <u>of said set</u> of claim 1 in said diagnosis.

11. (Amended) A method according to claim 10, comprising the step of using said DNA sequence for at least one of

(i) hybridization,

(ii) culture confirmation of isolated strains and,

(iii) chromosomal fingerprinting, and comprising the step of determining and differentiating at least one of cells, strains and types of mycobacteria and/or diagnosing mycobacterial infections.

12. (Amended) A method according to claim 10 comprising the step of differentiating at least one of cells, strains and species of virulent mycobacteria from non-virulent cells, strains and/or species.

13. (Amended) A method according to claim 10, comprising the steps of

(i) isolating cells, strains and/or species of at least one of the *M. tuberculosis* complex and other mycobacteria,

(ii) recovering crude or purified genomic DNA or RNA, and,

(iii) identifying a fragment that is identical or virtually identical to the sequence of the alanine dehydrogenase gene of *M. tuberculosis* (Fig. 2.3).

14. (Amended) A method according to claim 2 <u>or claim 10</u> comprising the step of diagnosing a clinical sample for tuberculosis in humans or animals.

15. (Amended) A method according to claim 2 carried out in the presence of substances that inhibit tuberculosis or mycobacterial infections of humans or animals and comprising the step of determining and recovering or making inhibiting substances.

16. (Amended) A method according to claim 10 used in at least one of

(i) antimycobacterial chemotherapy,
(ii) the control of epidemics and
(iii) after vaccinations (vaccination follow-up) in humans or animals.

17. A method according to claim 3 wherein the pathogen is *M. tuberculosis*.

18. A method according to claim 4 wherein the clinical sample is a body fluid.